

PATENT
1718-0218PUS1

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT: MARDH, Goran CONF: 2500
SERIAL NO.: 10/519,332 GROUP: 1623
FILED: December 23, 2004 EXAMINER: KHARE, Devesh
FOR: SYNERGISTIC INTERACTION OF ABACAVIR AND ALOVUDINE

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

May 29, 2007

Sir:

I, Dr. Lotta Vrang, Director of Bioscience at Medivir, Sweden, do hereby declare
the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am Director of Bioscience and have worked in the virology field for 30 years at
the Karolinska Institute, Astra and Medivir.

I am familiar with the above referenced patent application, as well as the
development, usages and properties of antiviral drugs, compounds and compositions.

I have read and understand the subject matter of the Office Action of November
28, 2006.

The following comments are offered in support of the patentability of the instant
invention.

Claim 1 is currently restricted to combinations with a weight ratio of 0.5 - 5 alovudine : 300 - 800 abacavir. In molar terms this means that the minimum ratio of alovudine to abacavir is 1:51. The significance of this high ratio is explained below.

The Examiner states that, based on the teachings in Margolis to combine abacavir (a guanine nucleoside) with a pyrimidine nucleoside, and the teachings in Harmenberg to combine alovudine (a pyrimidine nucleoside) with a guanine nucleoside, it would have been obvious to the skilled person to prepare a pharmaceutical composition comprising a combination of abacavir (a guanine nucleoside) and alovudine (a pyrimidine nucleoside). However a more comprehensive analysis of Harmenberg leads to the conclusion that it does not motivate the combination of alovudine and an alternative guanosine nucleoside.

It is noted that all the experimental results in Harmenberg are based on the combination of alovudine and the pyrimidine nucleoside, zidovudine. While Harmenberg refers to the purine nucleoside ddI, as shown in Table 1 of the present application the combination of ddI and alovudine is markedly less synergistic than alovudine in combination with abacavir, which is the combination being claimed. Note also that Harmenberg, for example at col 3, lines 43-49 stresses that for a synergistic effect, the 3'-fluorinated nucleoside such as alovudine should be administered approximately equimolar with the further nucleoside, with an outside boundary of 1:50 in molar terms. An equimolar formulation is a significantly different regime from the 0.5 - 5 mg alovudine to 300-800 abacavir that is claimed. The upper boundary of the alovudine range (5 mg) and the lower boundary of the abacavir range (300 mg) corresponds to a minimum ratio of 1: 51 in molar terms, based on a molecular weight of alovudine of 244 and abacavir 288.

If the skilled addressee was to endeavor to extend the teachings of Harmenberg to guanosine nucleosides, then even at Harmenberg's extreme limit of 1:50 coming nearest to the presently claimed ranges, the performance of the alovudine/ddG combination as proposed by the Examiner would lead away from the presently claimed combination. In particular in order to investigate whether a synergistic effect could be seen in a combination of alovudine and ddG as indicated in the Harmenberg patent, a study would be performed to evaluate the Combination Index value of alovudine and ddG. This study was conducted.

First, the ED and CI values were calculated as described in WO2004/002433, using a 1:50 ratio of alovudine and ddG. The results are summarized in the table below.

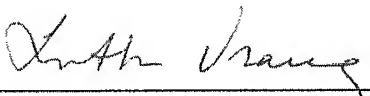
Combination	Molar ratio	Combination Index		
		50% inhibition	75% inhibition	90% inhibition
alovudine+ddG	1:50	1.14	1.59	2.23

These results show an CI above 1 for all three end points measured, namely EC₅₀, EC₇₅ and EC₉₀, which should be compared with the alovudine/abacavir combination in table 1 which shows an CI well below 1.

Based on the results of this study, I believe that the skilled practitioner, on reading the Harmenberg patent and carrying out a preliminary trial with an alovudine/ddG combination would not be tempted to extend the teachings of Harmenberg to another guanosine nucleoside.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 29 May 2007



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Education:

PhD, 1988
Department of Virology, Karolinska Institute, Stockholm "Studies on inhibitors of immunodeficiency virus reverse transcriptase"
Biomedical Scientist 1973

Work experience:

2000-present	Director of Bioscience Medivir AB, Huddinge, Sweden
1988-2000	Group leader, Senior Research Scientist – Bioscience Medivir AB, Huddinge, Sweden
1976-1988	Research Scientist, Anti-viral Chemotherapy Astra ALAB, AB, Södertälje, Sweden
1973-1976	Biomedical Scientist Department of Tumour Biology, Karolinska Institute, Stockholm

Publications:

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West SJ, Zhang H. Phenethylthiazolylthiourea (PETT) compounds as a new class of HIV-1 reverse transcriptase inhibitors. 2. Synthesis and further structure-activity relationship studies of PETT analogs. *J Med Chem.* 1996 Oct 11;39(21):4261-74.

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